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## Highly Resistant Cholera Outbreak Strain in Zimbabwe

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1 **Highly drug-resistant cholera outbreak strain in Zimbabwe, 2018 - 2019**

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3 Mashe Tapfumanei\*, MSc  
4 Ministry of Health and Child Care, Zimbabwe

5 Daryl Domman\*, Ph.D  
6 University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA

7

8 Tarupiwa Andrew, MSc  
9 Ministry of Health and Child Care, Zimbabwe

10

11 Manangazira Portia, M.D., M.P.H  
12 Phiri Isaac, M.D., M.P.H  
13 Ministry of Health and Child Care, Zimbabwe

14

15 Masunda Kudzai, M.D., M.P.H  
16 Chonzi Prosper, M.D., M.P.H  
17 Beatrice Road Infectious Diseases Hospital, Harare, Zimbabwe

18

19 Elisabeth Njamkepo, Ph.D  
20 Institut Pasteur, Paris, France

21

22 Masindi Ramudzulu, B.Sc (Hons)  
23 National Institute for Communicable Diseases, South Africa

24

25 Mtapuri-Zinyowera Sekesai<sup>‡</sup>, Ph.D  
26 Ministry of Health and Child Care, Zimbabwe

27

28 Anthony Marius Smith<sup>‡</sup>, Ph.D,  
29 National Institute for Communicable Diseases, South Africa

30

31 François-Xavier Weill<sup>‡</sup>, M.D., Ph.D  
32 Institut Pasteur, Paris, France

33

34 **Corresponding author:**  
35 F-X.W., Unité des Bactéries Pathogènes Entériques, Institut Pasteur, 28 rue du Dr  
36 Roux, 75015 Paris, France, [francois-xavier.weill@pasteur.fr](mailto:francois-xavier.weill@pasteur.fr), Tel +33 1 45688345

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38 \*These authors contributed equally; <sup>‡</sup>these authors jointly supervised this work

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45 TO THE EDITOR: From 6 September 2018 to 26 March 2019, Zimbabwe experienced a  
46 large cholera outbreak with 10,730 suspected cholera cases and 68 deaths (Fig. S1).  
47 Antimicrobial susceptibility data available on 65% (241/371) of the confirmed cases  
48 showed that the *Vibrio cholerae* O1 serotype Ogawa isolates were multidrug resistant,  
49 with unexpectedly high-level resistance to ciprofloxacin (96.7%, 233/241) and  
50 ceftriaxone (99.6%, 240/241). Details of the methods are provided in the Supplementary  
51 Appendix, available with the full text of this letter at NEJM.org. We sequenced the  
52 whole-genomes of 11 *V. cholerae* O1 isolates – including ten collected during the  
53 cholera outbreak in Zimbabwe, and one originating from a South African patient with  
54 travel history to Zimbabwe (Fig. S1, Table S1) – to investigate the determinants of  
55 antimicrobial resistance as well as their phylogenetic relationships to >1,200 global  
56 seventh cholera pandemic *V. cholerae* El Tor (7PET) genomes.<sup>1,2</sup> Phylogenomic  
57 analyses show that the 11 studied genomes belonged to sublineage T13 of the 7PET  
58 lineage (Figs 1A and 1B, Table S2). Sublineage T13 was recently introduced from  
59 South Asia into East Africa and from there to Yemen (Figs 1B and 1C).<sup>2</sup> The T13  
60 isolates were previously shown to have a narrow antimicrobial resistance (AMR)  
61 pattern, mostly due to a ~10-kb deletion in the SXT/R391 genomic island (called  
62 ICE *Vchl*Ind5), resulting in the loss of four AMR genes.<sup>2</sup> However, the 2018 Zimbabwean  
63 isolates differed from previous T13 isolates by having 14 additional antimicrobial  
64 resistance (AMR) genes carried on a ~160 kb IncA/C2 plasmid, leading to a broader  
65 resistance profile (Fig. S2, Tables S3-S4). In particular, the isolates were intermediately  
66 resistant or resistant to tetracycline (presence of the *tet(A)* gene), intermediately  
67 resistant or resistant to ciprofloxacin (mutations of the *gyrA* and *parC* genes and  
68 presence of the *aac6'-Ib-cr* gene) and produced a CTX-M-15 extended spectrum beta-

69 lactamase. Antibiotics such as tetracyclines, macrolides, and fluoroquinolones are  
70 commonly used in the treatment of moderate-to-severe cholera cases – as an adjunct to  
71 rehydration therapy – to shorten the duration and volume of diarrhea, thereby limiting  
72 bacterial transmission.<sup>3</sup> However, beta-lactams are not. Resistance to extended-  
73 spectrum cephalosporins (ESCs) is uncommon in 7PET isolates, and only ESC-  
74 resistant (ESC<sup>R</sup>) 7PET isolates from sporadic or small outbreak cases were observed in  
75 Africa before 2018.<sup>1</sup> It is noteworthy that a large typhoid outbreak (> 3000 suspected  
76 cases) caused by a ciprofloxacin-resistant strain – requiring the use of ESCs – occurred  
77 in Harare between October 2017 – February 2018.<sup>4,5</sup> This might have contributed to the  
78 ESC<sup>R</sup> patterns seen among the cholera outbreak strain several months later.

79 The 2018 Zimbabwean isolates were susceptible to azithromycin, which was  
80 consequently used to treat severe cholera cases during the outbreak. However,  
81 azithromycin resistance genes, such as *mph(A)* or *mph(E)* were sporadically identified  
82 in CTX-M-15-producing 7PET isolates collected in Zimbabwe (Table S4), the  
83 Democratic Republic of the Congo<sup>1</sup>, and Kenya<sup>2</sup> from 2010 to 2015. The acquisition of  
84 an IncA/C2 plasmid carrying both *mph* and *tet* genes by this T13 7PET strain would  
85 jeopardize the oral antibiotic treatment of cholera.

86 We emphasize the need for cross-border collaboration and continued laboratory  
87 surveillance to stemming this highly-drug resistant T13 cholera strain in Africa.

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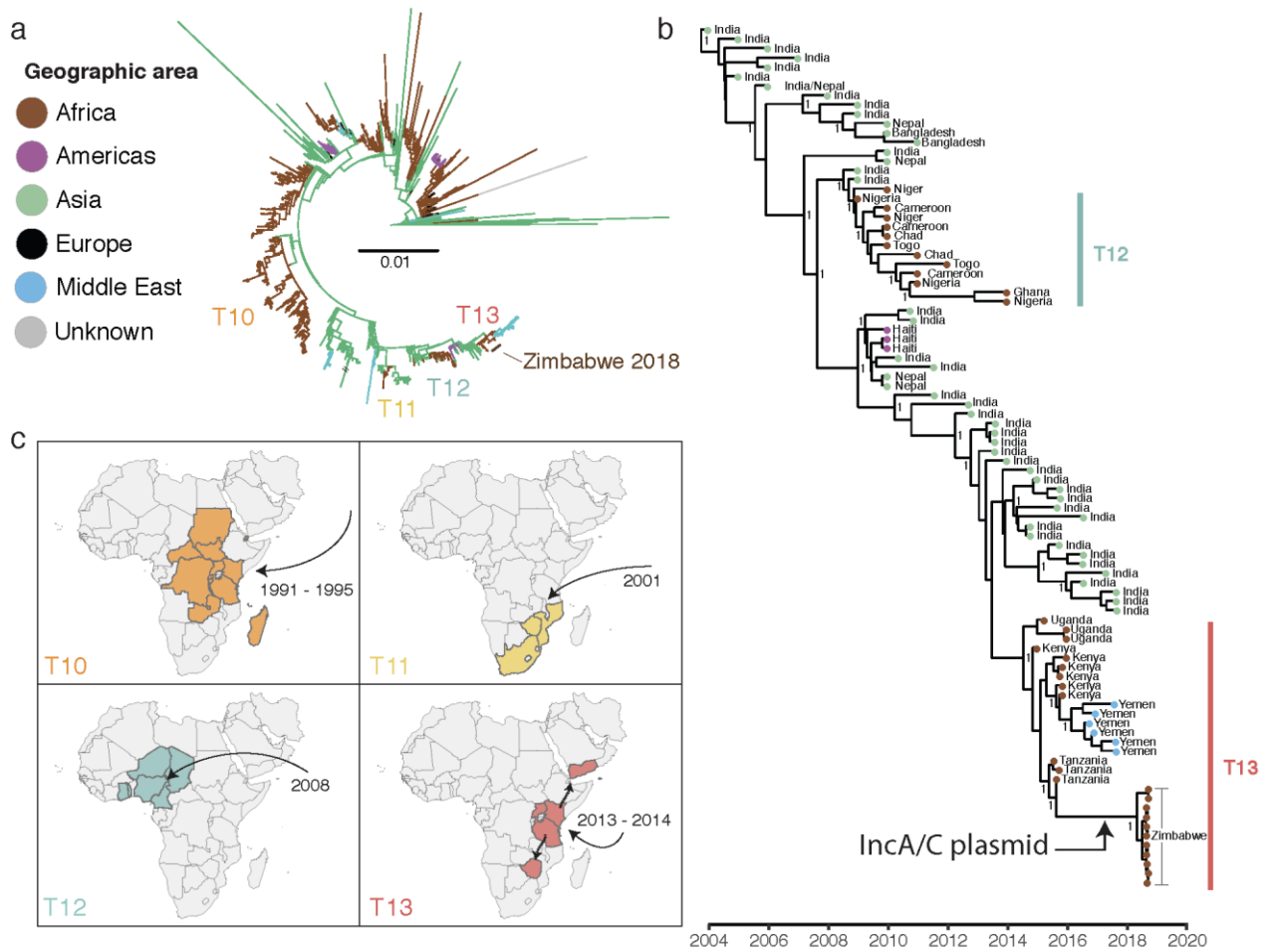
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109 **Legend to Figure**

110 Phylogenetic relatedness of the *V. cholerae* O1 El Tor isolates from the 2018 outbreak

111 in Zimbabwe. **a**, Maximum likelihood phylogeny of 1,213 genomic sequences. A6 was

112 used as an outgroup. The scale bar denotes substitutions per variable site (SNVs).

113 Branches are colored according to geographic location, inferred by stochastic mapping

114 of the geographic origin of each isolate onto the tree. The inferred introduction events

115 into Africa are indicated by the letter 'T'. One branch was artificially shortened and as

116 denoted by the hash mark. **b**, Maximum clade credibility tree produced with BEAST for

117 a subset of 92 representative isolates of the distal part of genomic wave 3 (i.e., those

118 with the *ctxB7* allele). Geographic location of the isolates is indicated in the same colors

119 as in panel **a**. Selected nodes supported by bootstrap values  $\geq 0.95$  are shown.

120 Acquisition of the multidrug-resistant plasmid is shown **c**, The geographical distribution

121 of selected 7PET sublineages T10 - T13. The date ranges shown for introductions are  
122 the 95% credible interval estimate of the MRCA in years. Dashed lines do not represent  
123 precise routes of transmission.

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